3rd Versus Arthritis: Pain Research in the UK Virtual Conference 2021

Meeting date: 14th July 2021

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Overview from Conference Chair

This 3rd annual conference by Pain Centre Verses Arthritis at the University of Nottingham on behalf of the charity, fulfilled its promise as an active and educational day of presentations, posters, workshops, and an excellent and thought-provoking double act in its plenary lecture by Professors Emily Jefferson and Tim Hales. The conference combined within its virtual setting, UK clinical and preclinical researchers in musculoskeletal and other forms of chronic pain. Workshop themes included Big Data, Pain measurement and assessment, Phenotypes, Molecular pain mechanisms and New approaches to treatment. The quality of posters and oral presentations was exceptional, and I congratulate Asta Tramholm for being voted the best oral poster presentation by delegates on the day. I look forward to seeing the new and consolidating collaborative networks that the meeting has nurtured by bringing together research leaders and early career researchers to discuss from across the UK. I hope that in some small way this conference will prove to have helped to shape future research efforts that will ultimately help us together to solve the problem of chronic pain. At the very least, I hope that all our participants had an enjoyable and productive day.

David Walsh
Conference Chair, co-director, Pain Centre Versus Arthritis at the University of Nottingham.

Workshop reports

The main aim of the workshops was to facilitate discussions in small groups on specific topics relating to pain, to develop collaborations, share and learn from other's experiences. Topics were selected by the Organising Committee based on submitted workshop topic proposals from the UK pain research community. Discussion within workshops was diverse and productive, with common themes overlapping between workshops. Brief summaries of discussion content are given below.

Workshop No	Workshop Theme	Co-chair	Co-chair	Facilitator
1	**Big Data**	Emily Jefferson (Dundee)	Tim Hales (Dundee)	Asta Tranholm
2	**Pain measurement/ assessment**	Cathy Price (Southampton)	Vicky Batchelor (Kennedy Oxford)	Vas Georgopoulos
3	**Phenotypes**	Frances Williams (KCL)	David Walsh (UoN)	Wendy Chaplin
4	**Molecular pain mechanisms**	Ewan St John Smith, (Cambridge)	Vicky Chapman (UoN)	Peter Gowler
5	**New approaches to treatment**	Jennifer Laird, (Lilly)	Nidhi Sofat (St Georges Uni London)	Dan McWilliams

Workshop 1 – Big data

Questions for discussion:

Q1. What are the main barriers to being able to access pain related data?
Q2. What is the most important pain data which is currently unavailable which you would like to see collected?
Q3. What can we do to improve the way pain is collected in routinely collected electronic health records?
Q4. How will big data help people living with pain?

Discussion points:

1. What are the main barriers to being able to access pain related data?
    - Relating to anonymisation of data and standardisation of data
    - Ways to ensure data are collected similarly
        - Are GPs classifying people's pain similarly?
        - Standardise data using algorithms to code data similarly
        - Teach data collection and standardised data collection at beginning of career for GPs
    - Need for standardised website where "all" data gateways could be incorporated together, with governance, streamlined access and coding datasets for comparison?
        - Currently, different sources of large datasets which people may not be aware of, huge benefits of a standardised site where data from different sites could be accessed

2. What is the most important pain related data which is currently unavailable which you would like to see collected?
    - Diverse cohorts are needed (also an issue of barriers)
        - Lack of diversity in clinical data collected
            - Participants being largely white European
            - Data collection being available to people of differing cultural backgrounds
    - Omics-data of acute to chronic pain, is this data available?
        - Twins UK is a resource, but larger databanks are needed too
    - What other data would we like?
        - Imaging data, but also just correlating data, such as imaging with omics data
        - An attempt to collect pain data to support existing imaging data is underway and ongoing
        - Raises the debate of one standardised website with streamlined access and standardised data through coding etc for easy comparison
    - Make human data and animal data comparable, as well as preclinical and clinical?
        - Different standards apply but algorithms and data storage/governance could be comparable - once again returning to the discussion of one standardised access point

3. What can we do to improve the way pain data is collected in routinely collected electronic health records?

- Access sometimes proves difficult
    - natural language development is difficult because accessing data introduces anonymisation issues
- Huge benefit to developing a feedback loop between research development and data collection with GPs
    - Perhaps a standardised questionnaire could be developed as well
- Specialist pain clinics to record data other than categorical - extend electronic records
- Datahub could contain a standardised questionnaire, comparable across cohorts, it was discussed how it should be spread to the wider community
    - Launch workshop at large conference, introduce small focus group with a panel to discuss and finetune output
    - Publication of recommended outcome measures like IMMPACT for pain also assists with standardisation
    - A central place to log standards would be beneficial for this as well
- People would like to see big data more accessible both in terms of how to find it and how to compare/use it

Workshop 2 – Pain Measurements and Assessments

Questions for discussion:

Q1. What are the current constraints on measuring outcomes?
Q2. What are the subtypes of pain that should be phenotyped when considering outcomes?
Q3. How can we better categorise differing pain phenotypes to enable clearer measurement?
Q4. What are the common methods to measure pain like behaviour in animal models?
Q5. What measures are representative of human pain phenotypes that can best represent differing human pain conditions

Discussion points:

1. Challenges measuring pain

- Clinical perspective: Time constraints to work with scales
    - Tool reliability issues
    - Lack of tools that could capture the entire picture in one session
    - Patient distress during clinic visits
    - Contextual factors: Language/Cultural barriers
- Research perspective: Time constraints for presurgical assessment through available tools (QST, MRI)
    - Limited data collection in one research-related visit
    - Long sessions needed to capture all aspects
    - Inability to conclude on pain mechanisms involvement through available tools
    - Duplication of assessment approaches

  - Problems with practicalities, ethics, data collection mediums and pragmatic scope of research
  - Lack of specificity and reliability of available tools
  - Degree of construct overlapping
  - Different patient cohorts (e.g., children) require different approaches of data collection
- Possible solutions:
  - Modern wearable take-away tech could help with data collection
  - Video instructions could also be implemented to help with research
  - Collection of data outside NHS (e.g., private practice)

2. Subtypes of pain that should be phenotyped

- Phenotyping/ stratifying might be more challenging than it seems
- Identification of stratification risk factors could be easier and more pragmatic
- There are no clear cut-offs between patients/participants
- Consideration about how psychometrically sensitive are available measurement tools

3. Can we better categorise differing pain phenotypes to enable clearer measurements?

- Phenotyping is a nebulous concept. Better classification methods should be developed
- Clear definition of the purpose behind phenotyping
- Difficulty to translate findings into clinical change
- Pain does not have a good link between pathology and symptomatology
- Traditional approaches of management and measurement of pain tend not to work very well.

4. What measures are representative of human pain phenotypes that can best represent differing human pain conditions?

- Animal models are often criticised, but it is the interpretation of the model that should be looked at
- Animal models can provide inference about specific mechanisms
- Tests can be biased towards identifying specific mechanisms rather than the multidimensionality of pain
- Most animal models are based on evoked pain rather than spontaneous pain.

Workshop 3 – Phenotypes

Questions for discussion:

Q1. What phenotypic characteristics or classifications do you use in your own research?
Q2. What phenotypic characteristics are most likely to advance our understanding and treatment of pain?
Q3. What would be the core phenotypic data that you would want to collect by all researchers in order to combine data from separate research studies/cohorts to answer to big questions for chronic pain?
Q4. What evidence is needed to justify pain phenotyping research?

Discussion points:
Discussion focused on measurement tools that may be useful to define phenotypes. Most of the discussion was around QST and mechanistic phenotypes. Phenotyping was generally seen as a research tool at present, rather than as of yet being validated for clinical use:

- It was agreed that QST use in the clinical setting is limited by:
    - Not easily standardised
    - Unproven clinical value
    - Repeatability could be low
- Use in the research setting depending on specific research question
- The DFNS was felt to provide useful indicators for the treatment of neuropathic pain and for detecting small fibre neuropathy, although alternative or additional QST modalities may be relevant to other types of pain (e.g. musculoskeletal).

One participant pointed to the use of EEG to help distinguish anxiety from pain in the postoperative setting
Patient reported outcome measures (PROMS) were of great use clinically – FDA/EMA view as gold standard patient-centred outcomes, for example from pharmaceutical treatments. However, PROMS may have limitations for use in mechanistic dissection

- Also need standardisation
- Need measures of validity
- Need evidence of benefit in clinical practice

It was agreed that:-

1. A Delphi process would be a good way to start defining core measures, the contexts in which they may be useful and setting standards.
2. A systematic review to determine best available evidence and the gaps in evidence would also be beneficial.
3. A broad focus to pain research should be maintained, including psychosocial factors and autonomic, metabolic and immune system involvement.

Workshop 4 – Molecular Pain Mechanisms

How do we identify clinically relevant targets for the treatment of pain?
Questions for discussion:
Q1. How do we select appropriate experimental models and experimental endpoints to identify and investigate the mechanisms of novel molecular targets for the treatment of pain?
Q2. How can we maximise the opportunities of recent advances of transcriptomic studies to identify novel targets for treatment?
Q3. How can we best validate targets arising from pre-clinical studies using human tissue?

Discussion points:

1. How do we select appropriate experimental models and experimental endpoints to identify and investigate the mechanisms of novel molecular targets for the treatment of pain?
    - The translational value of experimental models of pain

- Debated the value of having robust and reproducible models of experimental models and whether they are useful in mimicking the variability of pain seen clinically?
- Noted that similar injuries don't always lead to pain in people. Discussed the use of outbred rodents or other interventions that lead to greater variability in the pain models, or the study of the progression of pain phenotypes in the models which does show variability. Use biomarkers to stratify the animals
- Discussed the experimental endpoints and the clinical relevance, considered the breadth of behavioural endpoints not just reflex withdrawal responses, expand to affective / emotional behavioural endpoints. Discussed the utility of EMG methods to study muscle reflex responses in rodents and humans.
- It was raised that from the pharmaceutical sector perspective that target discovery starts with the person (human genetics, omics, pathophysiology, pathway analysis)- Then go to preclinical model to focus on potential mechanisms of the identified target

2. How can we maximise the opportunities of recent advances of transcriptomic studies to identify novel targets for treatment?
   - Discussed the utility of transcriptomic datasets
   - Importance of quality of the sample (with or without pain, control PM samples etc). Use of human cells, the reproducibility and quality of IPSCs was discussed and confidence in IPSCs representing the cells wanted.
   - Discussed the importance of association endpoints for interrogating these large transcriptomic datasets.
   - Discussed the benefits of longitudinal studies, difficult to get human tissue, and need for robust pain phenotyping to provide the associations
   - Discussed the difficulties in maximising the outcomes of these large datasets (bringing together people with the necessary skillsets, harmonisation with other transcriptomic datasets and that this needs strong partnerships with bioinformatic experts whilst keeping a close eye on the pathophysiology of the disease.

Workshop 5 – New Approaches to Treatment

Questions for discussion:

Q1. Measuring pain in the clinic
Q2. Early versus late – how can we detect patients early enough so you can break the cycle? Analogy to Alzheimer's or Rheumatoid Arthritis
Q3. What did the migraine field do well that other pain areas have not?
Q4. What should he approaches be for pain management?

Discussion points:

1. How best to measure clinical (human) pain?
   - Pain measurement instruments patient reported outcome measures (PROs) and clinical reported outcome measures (ClinROs)
     - Generic PROs across different pain etiologies? To simplify data collection
       - IMMPACT guidelines

        - Other scientific societies
        - Comparison with regulatory guidelines
    - Problem working in silos – core outcome set for disease, if added to general outcomes, burden on patients
        - Agree domains if can't align PRO's
        - Make more generalisable
        - Correlate same measures in different patient cohorts?
        - Nottingham – Oxford project step-up OA trying to harmonise different pain scales – need paired data from same people
        - Oxford – Harvard cross-correlation of pelvic pain – minor changes in wording significant
        - Pain data platform collection need to consider baseline demographics
    - Usefulness of clinical trial PROs in routine clinical practice? – converting to real life?
    - Problem in pain is condition/symptom complexity reduced to single score
    - VAS, Likert scale – do they perform well at ends of spectrum? – Reliability?
- Harmonising how do we do it?
- Biomarkers?
- Training for clinicians

2. Early versus late – how can detect patients early enough so you can break the cycle?
    - First encounter with pain service is critical. Especially for fibromyalgia, low back pain, neuropathy
    - Early diagnosis tools? biomarkers? Cohort studies, patient trajectories?
    - Patient is diagnosed with an acute issue, only over time it becomes clear its not
        - How does chronification of pain occur?
    - Non-specialists diagnosing in first instance
        - Routed to a pain service or talking service first? Need to think about psychosocial context
    - GPs and physiotherapists may be overwhelmed by chronic pain patients
        - Triaging tools can be used
    - What about those that don't present or aren't treated?
        - 'Grin and bear it' & stay at home
            - lack of access to medical care,
            - over focus of clinicians on disease without considering pain as an issue (assumption that inflammation resolution will solve pain…. but not always) ….and perhaps there are other pain mechanisms at play that you can't detect with current methods?
    - How do we translate preclinical knowledge of early onset of pain and persistence of pain after resolution of inflammation and injury to clinical practice?
        - Blood samples from FM patient's collection seeking a marker that correlates with preclinical
    - Patient trajectory longitudinal studies – tendency to exclude patients whose pain resolves

    - Knee pain versus no knee pain - Capex study in Nottingham – 30% resolved
    - OARSI?
    - UK biobank? Have diagnosis but not pain - so for conditions where pain is not a given or constant, then hard to unpick….
    - GP databases – medication and diagnosis records
- What already exists?
- Developing methods to route patients in clinical practice?

3. Multiple novel migraine treatments approved in last 5 years – what did the migraine field do well that others pain areas have not?

- Other areas have had less focus on relating changes in condition directly to actual pain symptoms
- Migraine is very clearly defined clinically
- Lots of early experimental medicine efforts in migraine patients
    - Joint pain has been explored in normal people, arthroscopy etc but we are not aware of specific studies to explore

Feedback

What did our delegates think……..

Our delegate feedback survey was circulated to all delegates via Teams link and email and we received a great response, receiving feedback from a third of our delegates. We really appreciate the time and effort our delegates made to provide feedback to allow us to make the event an even better success going forward. We provide a snapshot of comments here for you to view and the word cloud shows all the things you enjoyed about the day……

Q. Overall how would you rate this event?

Our delegates gave the event a score of **4.65/5**

Q. How well organised was the event?

Our delegates scored the organisation of the event **4.54/5**

Q. What would make this event even better for you in the future?

30% of responses said they would like the conference to be in person next time. Other comments included,

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“Maybe run over a day and half to allow participation in more sessions. Shorter poster sessions and more time for discussions”

“Being able to showcase my research, and learn about up-to-date research outside of pathology, animal models or microbiology”

“A broader focus on different research strands (i.e. experimental/psychological research)”

“space to network a bit more even virtually”

“I'll look forward to experiencing the conference in person, I think the organisers did a fantastic job especially considering the extra challenge of having to change the format! Massive thank you!”

“More oral presentations”

“Slightly more breaks”

“maybe the opportunity to join 2 workshops during the course of the day”

Thanks everyone for making this a great meeting and we hope you can all join us for the 4th Versus Arthritis Pain Research in the UK conference in 2022

PAIN CENTRE VERSUS ARTHRITIS
at the University of Nottingham